REMARKS

A response to the Office Action mailed November 23, 2004, was filed on May 23, 2005. For convenience, the arguments and amendments made in the previous response, along with a complete listing of the claims, are repeated herein, and additional comments are included.

Claims 38-68 are pending and under examination. Claim 39 has been amended. Support for the amendments can be found throughout the specification and the claims as filed. In particular, support for the amendment can be found, for example, on page 59, lines 5-9. Accordingly, these amendments do not raise an issue of new matter and entry thereof is respectfully requested.

Rejections Under 35 U.S.C. § 112

The rejection of claims 38, 41 and 42 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement is respectfully traversed. Applicant respectfully maintains that the specification provides sufficient description and guidance to enable claims 38, 41 and 42.

Applicant respectfully maintains, for the reasons of record, that the specification provides sufficient description and guidance for various routes of administration. With regard to targeting lymphoid tissues other than spleen, Applicant respectfully maintains that the Rule 132 Declaration by Dr. Zanetti filed in the response submitted July 29, 2003, corroborates Applicant's position. The Declaration indicates that a large percentage of the cells in various lymphoid tissues are B cells, including 10-15% in peripheral blood, 40-50% in spleen, 20-25% in lymph nodes, and 60-70% in Payer's patches. In the Office Action on page 6, it is acknowledged that spleen cells contain a large number of B cells. However, Applicant respectfully disagrees with the assertion that "other tissues, including other lymphoid tissues such as lymph nodes or peripheral blood do not." Clearly as discussed above and in previous responses, various lymphoid tissues contain a large number of B cells. To assert that 10-15%, 20-25% and 60-70% of cells being B cells in peripheral blood, lymph nodes and Payer's patches, respectively, is not a large number of B cells, whereas 40-50% in spleen is a large number of B cells, is not tenable.

Further in corroboration of the enablement of administration to a lymphoid tissue other than spleen, Applicant submits herewith as Exhibit A evidence that even a lower number of B

cells than the lymphoid tissues peripheral blood, spleen, lymph nodes and Payer's patches, can be successfully targeted to stimulate an immune response. Submitted herewith as Exhibit A is a manuscript by Rizzi et al., which is in press and co-authored by the inventor, Dr. Zanetti. The manuscript describes successful immunization *in utero* utilizing a plasmid vector containing a B cell expression element exemplified in the specification and as recited in the claimed methods. At the time of fetal development of the *in utero* administration (day 16), the fetal liver is the major site of B lymphopoiesis (see page 4 of manuscript, left column, lines 185-187). The manuscript indicates that $B220^+$ cells, a marker for B cells, account for approximately 3-5% of fetal liver cells whereas $CD19^+$ cells, also a marker for B cells, account for approximately 2% of fetal liver cells (page 4, left column, lines 193-195). Thus, the presence of less than 5% B cells in a fetal model of a lymphoid tissue resulted in successful immunization with a plasmid vector containing a B cell expression element. Applicant respectfully submits that the evidence presented in Exhibit 1 corroborates the enablement of the claimed methods.

Based on the presence of a large percentage of B cells in various lymphoid tissues, Applicant respectfully maintains that the expression in B cells exemplified by administration to spleen is enabling for administration to various lymphoid tissues, as attested to by Dr. Zanetti in the previously filed Declaration. Therefore, Applicant respectfully maintains that the specification, in combination with what was well known to those skilled in the art, provides sufficient description and guidance to enable the claimed methods.

Applicant respectfully maintains that the reference by Maloy et al., Proc. Natl. Acad. Sci. USA 98:3299-3203 (2001), which was submitted as Exhibit 2 with the response filed July 29, 2003, corroborates Applicant's position that administration to various lymphoid tissues is enabled by the teachings in the specification. Maloy et al. clearly demonstrates that administration of a nucleic acid vector to lymph nodes resulted in efficient expression of antigen and enhanced immunogenicity. Based on the description in Maloy et al. of superior immunity obtained by intra-lymph node injection, the utilization of a B cell promoter as taught in Applicant's specification and recited in the claims, and the presence of 20-25% B cells in lymph nodes, one skilled in the art would have had a reasonable expectation of successfully stimulating an immune response using the claimed methods.

To further support Applicant's position that Maloy et al. corroborates the enablement of lymph nodes as an exemplary lymphoid tissue, submitted herewith as Exhibit B is Castiglioni et al., Int. Immunol. 15:127-136 (2003). As described in Table 1 on page 130 of Castiglioni et al., the total number of dendritic cells in lymph nodes is very low, accounting for 0.8% of the cells in lymph nodes (see column under "C57BI/6," row "Total DC in LN," percentage shown in parentheses). Thus, Maloy et al. clearly demonstrate successful intralymphatic immunization, even when dendritic cells, accounting for less than 1% of the cells in lymph nodes, were targeted. As discussed above and in the Rule 132 Declaration by Dr. Zanetti filed in the response submitted July 29, 2003, B cells account for 20-25% of the cells in lymph nodes, more than 20-fold higher than the number dendritic cells in lymph nodes. Accordingly, Applicant respectfully maintains that Moloy et al. corroborates the enablement of the claimed methods for stimulating an immune response by administering a plasmid vector to a lymphoid tissue such as lymph nodes and expressing of one or more heterologous epitopes in a B cell.

With respect to the references by Deonarian, Exp. Opin. Ther. Patents 8:53-69 (1998), and Miller et al., FASEB J. 9:190-199 (1995), referred to in the Office Action, Applicant maintains, for the reasons of record, that unpredictability is not an issue with respect to the claimed methods. Applicant respectfully maintains any unpredictability for *in vivo* targeting and expressing genes as described in these general review articles is not applicable to the claimed invention because the claims explicitly recite that the heterologous epitopes are expressed in a B cell and are, therefore, directed to methods where the nucleic acids have been successfully targeted to a B cell and expressed by a B cell.

Applicant maintains that the specification provides sufficient description and guidance to enable the claimed methods. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

The rejection of claim 39 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite is respectfully traversed. Applicant respectfully submits that claim 39 is clear and definite. Claim 39, as amended, recites "administering B cells of said lymphoid tissue to an individual, wherein said B cells express said one or more heterologous epitopes." Applicants respectfully submit that claim 39 is clear as to which cells are administered and express one or

more heterologous epitopes resulting in stimulation of an immune response. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 103

The rejection of claims 39, 40 and 43-68 under 35 U.S.C. § 103 as allegedly obvious over Soo Hoo, U.S. Patent No. 5,891,432, in view of Banerji et al., Cell 33:729-740 (1983), is respectfully traversed. Applicant respectfully maintains that these claims are unobvious over Soo Hoo, alone or in combination with Banerji et al.

Applicant respectfully maintains, for the reasons of record, that Soo Hoo, alone or in combination with Banerji et al., does not teach or suggest the claimed methods or compositions. Applicant maintains that there would have been no motivation to combine the description in Soo Hoo with that of Banerji et al. to obtain the claimed methods or compositions, absent Applicant's teachings. Furthermore, Applicant respectfully submits that, even if one were to combine the description in Soo Hoo with that of Banerji et al., the claimed methods and compositions would not be obtained. In the previous Office Action mailed March 10, 2004, it was asserted that Soo Hoo described using myeloma or plasmacytoma cells and that myeloma and plasmacytoma cells are "transformed B cells." As discussed in the previous response, there is no mention in Soo Hoo of "myeloma."

Furthermore, Applicants respectfully submit that myeloma and plasmacytoma cells are plasma cell tumors, not "transformed B cells." In corroboration, submitted herewith as Exhibit 1 are pages 1165 and 1376 from Stedman's Medical Dictionary, 26th ed., Williams and Wilkins Baltimore (1995), giving the definitions of "myeloma" and "plasmacytoma." The definitions of myeloma and plasmacytoma clearly indicate that these cells are plasma cells, not B cells. As evidence that plasma cells are distinct from B cells, submitted herewith as Exhibit 2 are pages 212 and 216 of Kuby, Immunology, 3rd ed., W.H. Freeman and Company, New York (1997). These pages clearly show that plasma cells are differentiated from B cells but are not themselves B cells. Therefore, even if, *arguendo*, one were to combine the description in Soo Hoo with that of Banerji et al., at best one skilled in the art may have been motivated to use plasma tumor cells, that is, plasmacytoma (Soo Hoo) or myeloma (Banerji et al.). However, the combination of Soo Hoo with Banerji et al. provides no teaching or suggestion of using a B cell, as recited in the

claims. Accordingly, Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

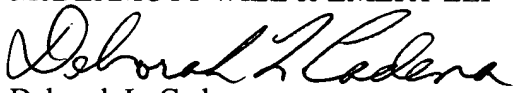
Applicants respectfully maintain, for the reasons of record and as discussed above, and as corroborated by the evidence submitted herewith, that Soo Hoo, alone or in combination with Banerji et al., does not teach or suggest Applicant' s claimed methods and compositions. Absent such a teaching or suggestion, Applicant maintains that the claimed methods and compositions are unobvious over Soo Hoo, alone or in combination with Banerji et al. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

In light of the amendments and remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully requests a notice to this effect. The Examiner is invited to call the undersigned agent if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

McDERMOTT WILL & EMERY LLP



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